

UNITED STATES NAVY *Medical News Letter*

Vol. 52

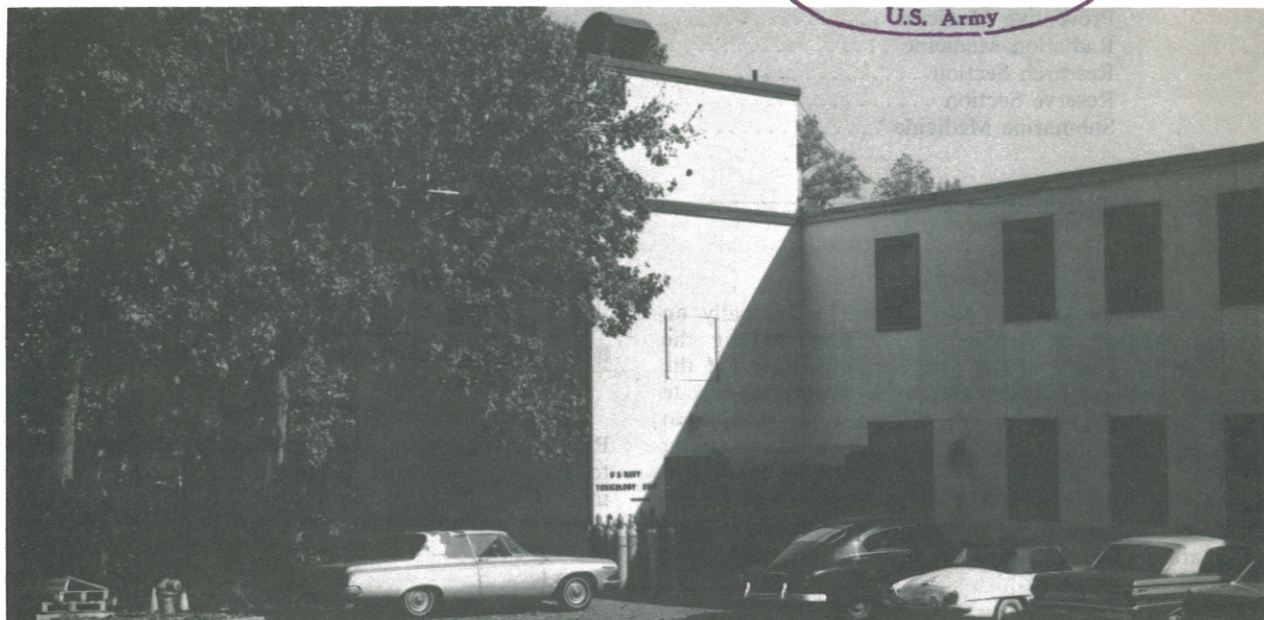
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United States Navy
MEDICAL NEWS LETTER

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No. 1

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ceptible to use by any officer as a substitute for any item or article, in its original form. All readers of the News Letter are urged to obtain the original of those items of particular interest to the individual.

Change of Address

Please forward changes of address for the News Letter to Editor: Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. 20390 (Code 18), giving full name, rank, corps, old and new addresses, and zip code.

FRONT COVER: NAVY TOXICOLOGY UNIT. The Navy Toxicology Unit was established on 1 January 1959 as a component command of the National Naval Medical Center, Bethesda, Maryland. Its mission is to provide technical and specialized service in the fields of operational toxicology and health engineering to solve toxicity problems encountered aboard ships and in the design and use of new weapons systems. NTU develops and provides the biological data needed to determine the safe permissible limits for toxic materials near which personnel may work, so that precautionary measures conducive to good health practice may be prescribed. Materials suspected of being potentially toxic are numerous and are under constant study in the laboratory or aboard ship. For example, this research group is studying the toxicity of trace contaminants in nuclear powered submarines. One of the materials of current interest is Dichloroacetylene. This was originally encountered as a degradation (or decomposition) product which appeared during anesthesia with Trichloroethylene. Several deaths were attributed to the decomposition product formed when Trichloroethylene passed over an absorptive agent such as soda lime. Tests made by the Navy Toxicology Unit place Dichloroacetylene in a highly toxic category. Its presence aboard submarines has been identified by the Naval Research Laboratory and poses a potential health threat to the crews of these vessels. The Committee on Toxicology of the National Research Council has tentatively recommended that to protect crews the level of this material be kept below 0.1 parts per million. Studies are underway that will develop basic data which more closely simulate submarine conditions. The Navy Toxicology Unit has made a significant contribution to the safety and efficiency of ship crews and others whose health may be threatened by varied types of potentially toxic substances.

The issuance of this publication approved by the Secretary of the Navy on 4 May 1964.

CLINICAL MANAGEMENT OF ASTHMATIC BRONCHITIS

SOME OBSERVATIONS ON 100 CASES

Robert G. Lovell, MD, Ann Arbor, Michigan, *Dis Chest*
53(1):50-56, January 1968.

The physician who works with pulmonary disease patients is impressed by the increasing number of young adults whose chief problem is progressive shortness of breath punctuated by episodes of wheezing, colored sputum and dyspnea associated with infection of the lower respiratory tract. For want of a better term, I shall call this "asthmatic bronchitis," recognizing that the nomenclature in this field is so confused as to create consternation among those who try to communicate with their colleagues.

A type of "infectious asthma" is seen in children who perhaps for a limited few months or years, experience wheezing, dyspnea and cough only when infection of the respiratory tract is present. Between infections, they are asymptomatic. I should like to confine this report to the condition in *adults* which at first resembles the infectious asthma of childhood. With the passage of time the wheezing and the dyspnea become progressively severe, eventually continuous, and are accompanied by a relentless and resistant infection of the bronchopulmonary tree. The pathophysiology of this disease is rather uniform, in that there is spasm of the bronchial muscles, with thickening of the basement membrane of the epithelial layer of the bronchi, and there is much mucus, cellular debris and purulent sputum in the respiratory passages.

The cause(s) of the bronchitis accompanied by wheezing in these patients may often be multiple. In some instances no etiology can be found. *Allergy* in childhood which has been dormant, and then becomes clinically active in adult life may be a factor. I have been impressed also by how often these patients give a history of having had *whooping cough*, *pneumonia* or *measles* with pulmonary complications during childhood. Some of the patients, and many are farmers or industrial workers, may have aggravation of their respiratory tracts by *occupational* and

environmental irritants. The possibility of air pollution as an irritant factor should be explored more extensively. A chief cause of asthmatic bronchitis must, of course, be chronic infection of the lower and sometimes also of the upper respiratory tract. That control of infection with antibiotics so often leads at least to temporary amelioration of the symptoms, supports the contention that *bacterial infection* is often involved. *Virus* etiology is less often encountered, but when present, the attacks respond poorly to most forms of treatment. There may be some inherent *genetic defect* which makes defense against infections less effective. None of this series had hypogammaglobulinemia. I cannot help but be impressed by the adverse effect which *cigarette smoking* plays in the aggravation and perpetuation of asthmatic bronchitis. That it may be shown to be one of the specific initiating causes in some cases, I think will be apparent eventually. The larger number of women now involved with severe asthmatic bronchitis can perhaps be accounted for by the change in their smoking habits. Since World War II, many women have become heavy cigarette smokers, using more than 15 cigarettes per day. Asthmatic bronchitis, extremely rare prior to the 1940's in women, as shown in the series under study, has now become as common in women as in men. Finally, there is a group of *idiopathic cases*, in non-smokers, where there is no clue as to the cause of onset of the repeated attacks which the patients experience. These are particularly perplexing, and because we have little or no information as to cause, we are forced to treat them symptomatically—usually rather unsuccessfully.

Diagnosis of asthmatic bronchitis typically is not difficult to make and the history is helpful. The patient, usually a healthy appearing young adult male, presents himself with the story of having a "cold" which has persisted longer than usual; it has caused

some dyspnea and a cough productive of yellow sputum. There is also wheezing which is aggravated by exertion, by coughing and other nonspecific irritants. About two-thirds of these patients are heavy cigarette smokers.

Examination of the chest reveals generalized inspiratory and expiratory wheezes, usually without crepitant rales. The remainder of the examination is normal. Clubbing of the fingers, or cardiac abnormality are rarely, or coincidentally observed.

The laboratory is not of great help except to assist in ruling out the possibility of other causes for cough—such as foreign body, pneumonia, tuberculosis, neoplasm, and pulmonary emphysema to name a few. Chest x-ray films may show some accentuation of hilar markings, but no pathognomonic signs. The white blood count is normal or mildly elevated. Pulmonary function studies including the timed vital capacity and maximum expiratory flow rate will be much reduced, showing both restrictive and obstructive changes, compatible with the findings seen in acute pulmonary emphysema or bronchial asthma.

With treatment, the patient with asthmatic bronchitis improves, especially with his first few episodes, and is able to resume work, but the distressing progression in frequency of attacks and in the slowing of the recovery time from each attack is seen over and over again in our cases. The patient's work record shows increasing absenteeism and finally he becomes unable to work. Unchecked, this disease may smolder for years flaring with each "cold"—and often requiring extensive medical care before being controlled again. It also is possible for the course of the disease to progress in a "malignant form" at an alarming rate, and in a matter of months the patient may become a permanent respiratory cripple, with continuous wheezing, cough and purulent sputum. Death often comes from one of the episodes of infection which seems to reduce further the already borderline capacity to support life. Occasionally death results from cardiovascular failure.

Management of the Patient With Asthmatic Bronchitis

It is very helpful for *one* doctor to follow the patient. In this way, optimal supervision is provided in a situation where it is easy for the patient to become discouraged and to give up. Furthermore, adequate follow-up visits are essential to the success of the program. Patients tend to wander from the medical regimen which, although imperfect, offers the best chance at present for control. The following steps are recommended:

1. *Complete cessation of smoking.* The realization that cigarette smoking is an aggravating factor in the disease of these patients has been a major step. Patients are being withdrawn from smoking and some are being rehabilitated and returned to work. Stoppage of all forms must be complete. We have found that abrupt withdrawal from smoking, with sedation and even the use of tranquilizers during the first weeks of abstinence will be successful if the patient is seen frequently by the physician, and the medical need for stopping smoking is explained.

2. *Control of environment.* Related to the adverse effect of smoking is the irritation caused by inhalation of dusts, chemicals, hot vapors and even frequent changes in temperature. The physician needs to assess the possible effect which such irritants may have on the respiratory tract of his patient and attempts must be made to protect him from them.

3. *Weight and general nutrition.* The obese patient is handicapped, and his weight must be brought under control so as to lighten the burden on the cardiovascular and respiratory systems. Proper nutrition is of course essential.

4. *Muscular development.* With muscular development, there is more efficient utilization of oxygen by the patient. Regular exercises must be taught, including mild calisthenics and slow muscle movement. Repeated walking at four miles per hour, sustained for two and one-half minutes daily with progressive increases has been shown to produce a decline in oxygen consumption six weeks after the exercises are started. Furthermore, training the patient to breathe *slowly* reduces his work oxygen cost. He is instructed to try for a rate of ten breaths per minute.

Ventilation Rate (Breaths per minute)

As the patient progresses with his exercises, he is observed to have a reduced respiratory rate and there is also a decline of heart rate. An additional asset is the observation that oxygen recovery is more rapid in the patient who exercises and has good muscle tone. His progress can be followed by recording his pulse and respiratory rate before and after a standard exercise, such as step-up tests. Vital capacity is checked, chest expansion is followed with a tape measure at regular intervals.

5. *Medication.* We have found that the routine and regular use of three medications has been very helpful: (a) antibiotics are given continuously at first in therapeutic levels for several months, and perhaps a sustaining dose is given for a number of years;

(b) bronchodilators (sympathomimetic amines and xanthine combinations) given every six hours regularly help to reduce bronchospasm and promote raising of secretions; (c) an expectorant, such as glycerol guaiacolate or saturated solution of potassium iodide given four times daily is useful.

Our antibiotic program routinely starts with tetracycline, since this broad spectrum drug has been so effective clinically against the gram positive cocci. Although it is difficult to make a blanket statement regarding the organisms isolated in patients with asthmatic bronchitis, usually only one predominant organism is involved. In the United States, mixed infection of all types is encountered in less than 2 percent of cases. Erythromycin is a good alternate drug, since over 90 percent of isolated organisms fall within its spectrum. Of the gram negative organisms, only 7.6 percent isolated were not susceptible to erythromycin. Of these, *Escherichia coli* responded best to polymyxin (87.2 percent); *Pseudomonas aeruginosa* best to polymyxin (83.3 percent); or to colistin (81.8 percent); *Klebsiella pneumoniae* to chloramphenicol (88.2 percent); *Bacillus proteus* to chloramphenicol (81.4 percent); and *Aerobacter aerogenes* to polymyxin (78.1 percent).

Penicillin, cephalothin (Keflin) and other antibiotics including triacetin oleandomycin (TAO) are resorted to after specific sensitivity studies. It has been our practice to place asthmatic bronchitis patients on therapeutic levels of antibiotics until the infection seems under control, then to reduce the dose by one-half and continue it on a daily basis rather than stopping the medication. The schedule is reviewed every few months and is changed according to the patient's progress.

The second feature of the medications—the bronchodilators—merits comment. Selection of the particular drug should be based on the patient's tolerance of it in regular four times daily doses. We prefer a combination containing aminophylline, a barbiturate and ephedrine, such as aminophylline, ephedrine, amobarbital (Amesec), theophylline, ephedrine, phenobarbital (Tedral), aminophylline, racephedrine, phenobarbital (Amodrine), or a similar preparation which also has included potassium iodide is theophylline, ephedrine, phenobarbital, potassium iodide (Quadrinal). A compound which contains the three active ingredients of all of the above, in which glyceryl guaiacolate is substituted for the iodide is theophylline, ephedrine, phenobarbital, glyceryl guaiacolate (Verequad). The essential feature of the program is to establish a blood level of the medication and then to sustain it for a prolonged period

of time. Constant review of the patient's medication program on his return visits will show that during periods of improvement, he will drop this part of the regimen, taking the bronchodilator only when he feels tightness in the chest. We re-emphasize to each patient the absolute necessity for continuous use of the medication, and this approach is sustained for the remainder of the patient's life. It is not unusual, particularly in the more-advanced cases, for us to introduce the regular use of epinephrine by injection to supplement the bronchodilating effect of the other drugs. Epinephrine (Sus-phrine) given at 8 to 12 hour intervals, has been helpful in bringing additional pulmonary function to the patient. By teaching patients to give their own injections on a regular schedule, it has been possible to keep them going to their places of employment for additional months or years.

The third agent used, namely expectorant medication, can be noted briefly. Adequate intake of water affords the best opportunity for proper flow of the mucous secretions of the bronchial tree. Without water, the other drugs are less effective. Iodide, as saturated solution of potassium iodide, ten drops four times daily is a helpful preparation. Glyceryl guaiacolate 100 mg four times daily may also be given.

The use of ACTH and the corticosteroids probably creates as many problems as it solves in the management of asthmatic bronchitis. We prefer to delay using them as long as possible until the disease has progressed so that the patient is threatened with having to become chair-ridden because of dyspnea, and therefore unable to earn a living. Then, after review of the program, steroid therapy is instituted. Sometimes, perhaps through relief of bronchospasm, or the general feeling of well-being which occurs, we are able to sustain the patient for additional months or years. All the problems inherent to the use of ACTH and steroids appear to complicate the lives of our patients, since even the smallest dose which will provide them a reasonable exercise tolerance may at times be larger than is bargained for.

6. *Aerosol medication.* Drugs delivered topically by aerosol have some advantage in that their direct effect on bronchial musculature—as with isoproterenol or epinephrine—can be observed. Also, some mucolytic effect is observed when one uses n-acetyl cysteine (Mucomyst) in aerosol spray. Patients are helped considerably by aerosolization of isoproterenol six drops of 1:200 dilution in 4.5 ml of saline. This is given four times daily. In this dilute form, using normal saline solution rather than water, it rarely irritates the respiratory tract.

7. *Allergy evaluation.* I should be remiss not to point to the important part which specific hypersensitivity plays in furthering the disease of at least some patients with asthmatic bronchitis. The presence of other allergic stigmata—hay fever, seasonal asthma, or allergic rhinitis should make one press for a full-scale allergy history, examination including skin testing, and institution of hyposensitization if there is good evidence that extrinsic protein allergy does exist.

8. *Injection therapy.* In addition to the allergy treatment just cited, we felt that regular use of bacterial (catarrhal) vaccines, and virus vaccines such as a combination of adenovirus and influenza virus (Resprogen) when available, are useful, and in some patients they may influence favorably frequency of the infections. Gamma globulin injections, although disappointing in some, may be tried in patients who continue to have serial infections in spite of all measures. The benefit, if any, does not seem to be related to the patient's serum levels of gamma globulin prior to or subsequent to this treatment.

9. *Adequate follow-up.* Part of the success of the program for sustaining the patient with asthmatic bronchitis is based on establishing a good relationship with him. He must be encouraged not to give up. The motivation he can muster is the greatest stimulus to his rehabilitation. At all costs, he must be kept working—at least part-time if possible. If his disease is beyond recall and he cannot work, the attitude of trying to get well enough to resume *some* work is emphasized.

All patients, even those doing well, should be seen at regular interval visits. Problem cases are brought back weekly; the very good patients who cooperate and take their medicine well and who have evidence of improving, pulmonary function should be seen every two or three months on an indefinite basis.

Study of 100 Patients With Asthmatic Bronchitis

One hundred adult patients with the diagnosis of asthmatic bronchitis who have been on the above program were drawn in sequence from the files and categorized as to sex, history of childhood or serious illness which might have predisposed them to lung damage—such as pertussis or pneumonia, the use of tobacco, and present state of activity. Also, incidence of atopy was determined. As controls, the first 100 cases in the files of adults with atopic disease were studied in a similar fashion. The results are shown in Table 1.

TABLE 1

	Adult Allergy Patients	Asthmatic Bronchitis Patients
Sex		
Men	37	47
Women	63	53
Childhood or serious illness		
History—pertussis	42	47
History—measles	95	97
History—pneumonia	26	52
Presence of atopic disease	100	72
Use of tobacco		
Smoker	45	67
Non-smoker	55	33
Activity		
Alive, working	100	Working 78 Unable to work 12 Dead 10

Results

As would be expected, there were about twice as many women as men in the allergy control group. This 2:1 woman patient ratio is commonly observed in allergy practices. The asthmatic bronchitis series shows about equal men to women representation. The increasing number of women with asthmatic bronchitis, noted previously, over that seen 20 years ago is evident here.

Significantly more of the asthmatic bronchitis patients had a history of one or more bouts of pneumonia (52 compared with 26 in the controls). Also, two-thirds of them were cigarette smokers, using from five cigarettes to three packages per day. About one-half of the allergy patient controls smoked.

Seventy-two of the bronchitis patients had some evidence of atopy, either seasonal bronchial asthma, perennial extrinsic asthma, allergic rhinitis or urticaria. This is rather a high incidence, since in a cross-section of population, one might expect to find history of atopy in perhaps 25 percent of individuals.

A surprising finding was that 33 of the 100 asthmatic bronchitis patients did not smoke. Review of the records of these non-smokers showed that 19 of them had reported from one to five episodes of pneumonia. Of the remaining 14 non-smokers, however, six had no history of lung disease or allergy. Their occupations were considered innocuous (teacher, housewife, nurse, director, student and machinist). Thus, there was no observable predisposing cause for the lung disease in these six.

Study of the activity status shows that over the five-year period of observation, in spite of the therapeutic measures employed, 12 patients were disabled sufficiently to prevent their working, and ten were dead from their disease. There is indication that

more patients will become disabled in this group before long.

Discussion

Asthmatic bronchitis is one of the prime causes of pulmonary disability in adults in England. It is an epidemic problem in the United States. Our means for controlling this disease are hampered by several factors. We do not know the exact etiology. We suspect that cigarette smoking is an important aggravating factor, yet efforts to curtail the use of tobacco by the young—some of whom will be our patients in 15 or 20 years—are met by actual opposition, or indifference from many parents, educators (who have been repeatedly bombarded by health campaigns of every sort) and by government agencies. The medical profession fortunately has in general supported all measures to prevent youngsters from acquiring the habit of smoking. Over 50 percent of physicians in the United States now do not, or no longer smoke cigarettes, according to a survey completed in 1965. The gentle admonition now printed on each package of American cigarettes is a sad testimonial to the work and findings of the Surgeon General's Commission on the Effect of Smoking on Health. How successful the education programs being set up to combat smoking are, may well determine the incidence of asthmatic bronchitis in 1976 and 1986. The United States Public Health Service has reported that 11 times as many smokers as non-smokers die of lung cancer and 12 times as many die of emphysema. Statistics are not yet available to delineate

asthmatic bronchitis. More physicians must become concerned about the adequacy of therapy in pneumonia, chronic bronchitis and other smoldering lung diseases. Insufficient antibiotic therapy over too short a period of time is a commonly observed shortcoming in management of these patients in retrospect. Vigorous efforts to prevent progression of asthmatic bronchitis in affected patients are justified. It is hoped that better measures will be developed in the future so we can accomplish this.

Summary

The increasing and alarming incidence of asthmatic bronchitis, and its accompanying disability, morbidity and common progression to fatal illness requires intensive efforts to learn more about the disease. Of the patients with asthmatic bronchitis studied, two-thirds were found to be smokers, and over one-half had a history of whooping cough or pneumonia. The incidence of atopic disease in this group was 72 percent, a high figure in comparison to the general population. In six patients there was no history of previous lung disease, and there was no explanation for their development of asthmatic bronchitis.

The measures at hand for treating asthmatic bronchitis are discussed; in spite of them, the total disability and mortality of this group over a five-year period is 11 percent, ten patients having died.

(The omitted figure and references may be seen in the original article.)

LEAD POISONING ORALLY IN A PAINTER, WITH HEMATEMESIS

Azad Katchian, MD, J Occup Med 10(2):89-91, February 1968.

Lead intoxication by the oral route in adults is exceptional, although this is the usual mode of poisoning in infants and toddlers. Its occurrence specifically among painters is not mentioned in recent textbooks or other literature. Two authors on occupational medicine do consider it, only to deny it any clinical significance. Moreover, none of these sources reckon hematemesis as a possible manifes-

tation of lead poisoning. The following case, however, presented both of these features.

Report of a Case

A 26 year old white painter vomited about one-half pint of blood on August 12, 1965. The following day he was brought for medical aid because of colicky abdominal pain and diarrhea. Stuporous and at times incoherent, between paroxysms of abdominal pain he also complained bitterly of aching shoulders.

From the Department of General Practice, Bellaire Clinic, Bellaire, Ohio. Case presented at staff meeting, Bellaire City Hospital, October 8, 1965. Reprint requests to 4211 Noble Street, Bellaire, Ohio 43906 (Dr. Katchian).

He had not previously suffered from dyspepsia. His gum margins revealed a prominent line of pigmentation. There was diffuse hyperesthesia of the abdomen without localization or guarding. Hemoglobin was 12.2 Gm. %. Basophilic stippling was not noted. Urine test for coproporphyrin III was strongly positive. Initial lead values were 0.156 mg. per 100 ml. of blood and 0.560 mg. per total 24 hr. urine volume. Initial cerebrospinal fluid pressure was 240 mm. The fluid contained 9 polys and 1 lymphocyte per ml. A flat film of the abdomen revealed no abnormality. The abdominal pain subsided following intravenous administration of calcium gluconate. His mental state and hyperesthesia appeared to improve promptly following lumbar puncture. Pending the report on the initial analyses of blood and urine lead content, recurrence of symptoms was prevented satisfactorily by calcium carbonate and sodium citrate taken orally.

De-leading was then undertaken by means of standard courses of calcium disodium edetate (CaEDTA), 1 Gm. intravenously during a period of one hour every 12 hours. They were administered during the last three days of each week while the patient resumed his occupation during the remaining four days. Resultant blood and urine lead values are shown in Table I. His symptoms disappeared completely by the end of the second course. The "lead line" went more slowly but had also disappeared by the end of the eighth and last course. His hemoglobin then had risen to 14.0 Gm. %.

TABLE 1.—Relation of Blood and Urine Lead Content to Treatment with CaEDTA

Date	Blood mg/ 100ml	Urine mg/ total * 24 hr.	Remarks
8-20-65	0.156	0.560	Initial figures
8-29	—	2.250	Following course #1 with CaEDTA
9-6	0.088	1.420	Following course #2 with CaEDTA
9-28	0.031	2.300	Following course #3 with CaEDTA
10-12	0.031	1.290	Following course #4 with CaEDTA
11-8	—	—	No tests followed course #5.
11-26	—	1.120	Following course #6 with CaEDTA
12-6	—	0.547	Following course #7 with CaEDTA
12-29	—	0.085	Following course #8 with CaEDTA

* Determined on a 100 ml. aliquot of 24 hour urine.

The route of poisoning seemed obscure initially. Throughout his three years as a painter he had worked only outdoors. Although he had, indeed, used lead paint most of the time, it had always been ready-mixed rather than in powder form. He spe-

cifically denied using a spray gun, or burning, scraping, or sanding old paint during the period immediately prior to his illness. Further inquiry, however, revealed that he was both unusually talkative with his workmates and an inveterate gum chewer. Also at the end of the workday he customarily spent considerable effort in peeling the dried paint from his lips. It, thus, became evident that splashing paint had had ready access to his oral cavity.

Since his return to work he has used a face mask regularly. More than a year has now elapsed since the conclusion of his de-leading and he has remained well.

Comment

The Oral Route in a Painter. In days gone by a painter mixed his powder of lead pigment into the liquid medium. Since the abandonment of this practice lead poisoning in painters by inhalation, a route far more quickly poisonous than the oral, has to a large extent been reduced. (Sanding or flaming old lead paint in a confined space could still poison such a worker by inhalation.) But is a painter, working with lead in its "fixed" state, at no risk from poisoning by ingestion? Hunter, and Fleming have both answered the question in the negative. The present case shows that view to need change.

Contributing to the poisoning in the case here reported were the facts that the taste of the paint was not objectionable, and the patient had not been warned of the hazard. As to the taste of lead paint, testimony is also available from the best of experts—the pediatric patient. Talkativeness, gum chewing or smoking by painters during their work can be presumed to be common. Hence, painters should not only receive warning of danger, but receive it pointedly and impressively. The protective device need be no more cumbersome than a cover for the mouth alone.

Hematemesis as a clinical manifestation of lead poisoning appears not to have been recorded previously. However, pathologic changes in the gastric mucosa have been described: "In the earlier literature on plumbism, references are made to such pathologic changes in the intestinal tract as gastritis, necrosis of the gastric epithelium and other pathologic conditions. More recent authorities, however, have not noted such changes." The present case would seem to fill this clinical void.

Summary

Unwittingly ingesting lead paint during his job over several years, a painter developed hematemesis in addition to the full gamut of classical symptoms of lead poisoning. The need for impressing painters

of this risk is pointed out, and also its prevention by the use of a simple mask for the mouth.

(The references may be seen in the original article.)

UNUSUAL ASPECTS OF HYPERPARATHYROIDISM

*Henry Mannix, Jr., MD, FACS, and Walter J. Loehr, MD, New York, New York,
Surg Gynec Obstet 126(2):347-351, February 1968.*

The incidence of primary hyperparathyroidism is more common than has been suspected in the past. The more usual symptoms of hyperparathyroidism are those related to renal calculi and osteoporosis. These manifestations are well recognized, and patients with these conditions are usually evaluated with regard to calcium and phosphorus metabolism. Other less well recognized, but important, manifestations of parathyroid hyperfunction include parathyroid crisis, neonatal tetany in the offspring of a mother with parathyroid overactivity, peptic ulcer disease, and polyglandular endocrinopathy.

In reviewing the recent experience at The New York Hospital-Cornell Medical Center, we were impressed with the relative frequency of these less well known signs. Because relatively little attention has been given to these problems, it seemed worth while to evaluate and report our experience and to emphasize some of the points with regard to diagnosis and treatment. Another reason which prompted this study was the high mortality and morbidity connected with some of these symptoms if the diagnosis is not promptly established.

Parathyroid Crisis

In 1923, Dawson and Struthers first reported upon a patient with acute primary hyperparathyroidism which was rapidly fatal. Other investigators have since reported about 70 patients with so-called parathyroid crisis or parathormone intoxication.

Unlike the more common chronic form of hyperparathyroidism in which the sex ratio is about 2 females to 1 male, the incidence in this acute variety is equally distributed between the sexes. These individuals exhibit marked personality changes and

may go into a coma. The marked hypercalcemia may produce headaches, fatigability, nausea, vomiting, or dizziness. The increased excretion of calcium is associated with mobilization of large quantities of water. This may be reflected in symptoms of polydipsia and polyuria. Death, when it occurs, is usually secondary to cardiac arrhythmias.

Most patients in whom a parathyroid crisis develops have been found to suffer from the chronic form of the disease prior to the onset of the acute process. Frequently, immobilization in bed during evaluation of the chronic parathyroid condition has been the precipitating factor in the so-called parathyroid crisis.

At The New York Hospital 3 patients with this condition have been treated during the past 2 years.

Patient 1. An 80 year old Negro woman had a 2 year history of increasing pain in the knees and thighs. Eighteen months prior to admission, she was given a thyroid extract for a documented hypothyroid condition. The dosage was progressively diminished and finally discontinued 5 months before admission because of complaints of palpitations and fatigue. Serum calcium drawn at that time was 12.1 milligrams percent; serum phosphorus was 1.8 milligrams percent.

She refused further evaluation at that time, but because of increasing fatigue, polydipsia, and polyuria, she later consented to admission. Serum calcium on admission was 13.6 milligrams percent; serum phosphorus was 1.9 milligrams percent. Roentgenographic studies revealed generalized osteoporosis with cystic bone changes in the right femur compatible with hyperparathyroidism. No renal dysfunction was evident.

During hospitalization, the serum calcium level rose rapidly to a peak of 19.8 milligrams percent; concomitantly, she became increasingly lethargic and disoriented. She began vomiting and became

From The Department of Surgery, The New York Hospital-Cornell Medical Center, New York.

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incontinent. A regimen of hydration, electrolyte replacement, and infusion of ethylenediamine-tetraacetic acid was effective in suppressing the serum calcium level to 11.8 milligrams percent, after which she underwent removal of a parathyroid adenoma weighing 6.1 milligrams.

The postoperative course was uncomplicated, and she was subsequently discharged in satisfactory condition.

In the group of patients with parathyroid crisis, in which the fatalities are most frequent, the diagnosis may be difficult. Lethargy, weakness, back pain, and personality changes are so nonspecific that it may require considerable acumen to make the diagnosis. Fortunately, once the diagnosis has been considered, it is readily established because of the very high elevation of serum calcium and the low levels of the serum phosphorus. We do not believe that any procrastination is justified in such patients. Some may well benefit by aggressive hydration which may decrease the serum calcium levels to a less dangerous proportion, with correction of concomitant electrolyte imbalances. Goldsmith, Payne, and Chakinskian and their associates have demonstrated the usefulness of phosphate solutions, ethylenediamine-tetraacetic acid, sodium sulfate, sodium phytate, and even peritoneal dialysis as emergency measures in reducing serum calcium levels in parathyroid crisis as well as in other disorders producing a toxic hypercalcemia.

Results with phosphate infusion especially have been quite striking with little, or no, adverse effect. These measures should be regarded as only temporary, and these patients should be operated upon on an emergency or semiemergency basis. Coffey and his associates reported the death of a patient in whom operation was delayed overnight. Death was presumed to be due to a direct toxic effect of calcium on the myocardium. Since most of these patients have relatively large tumors, the surgical challenge is not usually great. At operation, most of them are found to have chief cell adenomas.

Neonatal Tetany

A rare and striking group of symptoms is presented by an infant with neonatal tetany. Probably less than 15 instances of the mothers with primary hyperparathyroidism who bear children with neonatal tetany have been reported in the literature since Friderichsen described the first such patient in 1938.

The causation of this syndrome is not well defined. It has been postulated that maternal parathormone may cross the placenta and suppress the glands of the infant. A second view holds that maternal calcium crosses the placental barrier and that the resultant increase in serum calcium in the infant suppresses the glandular function.

Tetany in the newborn is sometimes precipitated when mother's milk is replaced by cow's milk with its high phosphate load. In most patients, the tetany begins spontaneously at about 1 week of age. It is known that not all children with neonatal tetany are the progeny of mothers with hyperparathyroidism, and this clinical entity may not be suspected, unless calcium studies are carried out. These patients bearing children with neonatal tetany may have few, or no other, symptoms of parathyroid dysfunction, and a high index of suspicion is of prime importance in establishing the diagnosis.

One such patient has been treated at The New York Hospital.

Patient 2. At age 14 years, this female suffered the first episode of pain in the flank associated with hematuria. Diagnosis of renal calculus was made at that time. She gave birth to her first child at the age of 31 years. At 1 week of age, tetany developed in the infant. At age 32 years, this patient passed another renal stone. At ages 34 and 35 years, she gave birth to 2 more children, in whom neonatal tetany developed. At age 35, the diagnosis of primary hyperparathyroidism was initially made. During this same period, symptoms of peptic ulcer disease developed which responded to medical therapy. At age 36, she underwent exploration of the neck, with removal of a parathyroid adenoma; at operation, only 3 parathyroid glands were identified. At age 37, she gave birth to her fourth child, in whom neonatal tetany also developed.

At age 38, she was first seen at The New York Hospital. Serum calcium at that time was 13.6 milligrams percent. Serum phosphorus was 1.9 milligrams percent. Skeletal survey revealed generalized osteoporosis with subperiosteal bone resorption in the fingers. At exploration, an adenoma was found in the right inferior parathyroid gland, the one gland that had not been previously identified. The postoperative course was uneventful.

In those patients whose children have neonatal tetany, evaluation of serum calcium and phosphorus levels will usually lead to the proper diagnosis. These patients may well have small tumors and present technical difficulties at operation; but, thus far, the

patients reported upon have been young and rarely had significant renal abnormalities. Therefore, the operative risk is generally minimal.

Although most instances of tetany in the newborn period are due to causes other than hyperparathyroidism in the mother, maternal serum calcium and phosphorous levels should be determined, together with 24 hour urine collection of calcium excretion, as screening procedures for the condition.

The differential diagnosis of neonatal tetany includes hyperventilation and vomiting, both of which result in alkalosis with a subsequent decrease in serum calcium. No underlying disease process can be identified in most patients with tetany. In tetany in the newborn, regardless of the cause, the calcium level will be decreased and will, therefore, be of little value in differential diagnosis.

Peptic Ulcer Disease

An increased frequency in the occurrence of peptic ulcer disease in patients with primary hyperparathyroidism has been described by Choslark and Athe. In most reports, the incidence ranges from 9 to 16 percent. The ulcer disease found in hyperparathyroid patients does not appear to differ from that in other ulcer patients; levels of gastric acidity are similar in both groups. In most reported patients, the symptoms of ulcer disease precede those of typical hyperparathyroidism. Certainly, in this group, the mechanism is not clear despite careful studies carried out by many observers. Parathormone administration increases gastric secretions but does not change calcium levels. Spiro has shown that calcium levels below 6 to 7 milligrams percent are associated with a marked decrease in gastric secretion. He believes that adequate serum calcium is necessary for gastric secretion and that parathormone exerts primarily a permissive effect of acid and pepsin secretion.

Menguy and Masters, meanwhile, have shown that parathyroid hormone extract increases the mucous content of the stomach in rats and acts in a manner opposite to that of cortisone, which depletes the gastric wall of its protective mucous coat.

The incidence of peptic ulcer disease in patients with primary hyperparathyroidism at this hospital is comparable to that in other reported series, although it is difficult to determine accurately a clear-cut relationship between the 2 disease processes in many patients.

Patient 3. A 51 year old white male had passed his first renal stone at age 27 years; he passed a second stone at age 44. At age 50, symptoms of

peptic ulcer disease developed which were confirmed by roentgenologic studies. Treatment with a gastric diet and alkali resulted in only partial relief of the symptoms. During this period, the serum calcium was found to be 13.4 milligrams percent; serum phosphorus was 2.8 milligrams percent. In the 4 months prior to hospitalization, he noted an increasing weakness and fatigue which was associated with a 15 pound weight loss.

Laboratory studies on admission included serum calcium of 12.2 milligrams percent and serum phosphorus of 2.6 milligrams percent. Results of roentgenographic examination of the bones were negative. Results of an upper gastrointestinal series revealed a markedly deformed duodenal bulb.

At exploration, a single small parathyroid adenoma was removed. The postoperative course was uncomplicated. Serum calcium and phosphorus levels returned to normal, and he had no further symptoms from the peptic ulcer disease.

It may be that peptic ulcer disease has a still undisclosed relationship with hyperparathyroidism. Frame and Haubrich have reported a series of 300 patients with peptic ulcers screened for hyperparathyroidism, and 4 instances were found, 1.3 percent. They described some difficulties in evaluating serum calcium and phosphorus levels in these patients because of dietary regimens used in active ulcer patients and suggested that other diagnostic tests be utilized.

Polyglandular Endocrinopathy

The final group of patients includes those who suffer from polyglandular endocrinopathy. In this condition, a wide variety of multiple endocrine abnormalities have been reported, and all of the endocrine organs have been involved. We encountered 3 such patients.

Patient 4. Symptoms of peptic ulcer disease in this 46 year old white female developed at age 41 years. Symptoms were only partially relieved by a strict regimen of medical therapy. At age 44, she underwent subtotal gastric resection with gastrojejunostomy for a penetrating gastric and a duodenal ulcer. Three months later, a re-exploration was carried out for a perforated marginal ulcer which was plicated. She continued to suffer from the peptic ulcer diathesis, despite vigorous medical therapy. Results of an upper gastrointestinal series 6 months after the last surgical procedure showed a recurrent gastric ulcer. Occasional episodes of upper gastrointestinal bleeding were treated by transfusions.

At age 46, during hospitalization for intestinal bleeding, she was found to have a serum calcium of 12.6 milligrams percent, with a concomitant decrease in serum phosphorus to 2.2 milligrams percent. Results of a skeletal survey showed diffuse osteoporosis with cystic bone changes in both femurs. The 24 hour gastric acid secretion remained markedly elevated. Presumptive diagnosis of hyperparathyroidism was made, and she underwent exploration of the neck with removal of 3 hyperplastic glands. Serum calcium levels returned to normal but gastric acid secretion remained elevated. Abdominal exploration was carried out 1 month later, with resection of multiple pancreatic adenomas, revision of the gastroenterostomy, and vagotomy. The pathologic report concerning the pancreatic tissue revealed multiple islet cell adenomas.

Thereafter, the peptic ulcer disease remained quiescent, but the serum calcium level steadily increased during a 2 year period to a high of 14.1 milligrams percent with concomitant serum phosphorus of 2 milligrams percent. A re-exploration was carried out when she was 48 years old with removal of the only remaining parathyroid gland.

Postoperatively, there has been no further recurrence of hyperparathyroidism.

Patients with polyglandular endocrinopathy may pose some difficulty in diagnosis, since they rarely have typical symptoms of parathyroid disease when first seen. Serum calcium levels may be unreliable because of the effect of associated endocrine abnormalities or of the treatment of these associated disorders. It must be emphasized that clinical alertness is of prime importance in establishing the diagnosis. The basic pathologic condition of this disorder is usually hyperplasia, as was true in 2 of the 3 patients seen. The fact that in 1 patient a second exploration was required when only 3 of the 4 hyperplastic glands were removed initially impels us to believe that at least $3\frac{1}{2}$ glands should be excised. This may present some technical difficulty, since the hyperplastic glands rarely are increased in size.

Differential Diagnosis

Several well known conditions produce an increase in serum levels of calcium but do not act primarily through parathyroid hyperfunction. These states include metastatic carcinoma to bone, sarcoidosis, milk-alkali syndrome, and chronic renal disease.

A different group of patients with hypercalcemia has been reported in recent years in which the elevated calcium level appears to be produced by a parathormone-like substance secreted by tumors of nonendocrine origin—usually hypernephroma or lung carcinoma.

The symptoms in this condition are indistinguishable from those of primary hyperparathyroidism but, on exploration of the neck of these patients, hyperplasia of the parathyroid glands is rarely evident. Indeed, a transient period of hypocalcemia, which commonly follows removal of the neoplasm producing the syndrome, would indicate that the tumor suppresses normal parathyroid function.

In this group of patients, correction of the calcic disorder requires treatment of the primary tumor, and palliative surgery of the parathyroids offers little relief of the condition.

Summary

Unusual, but important, manifestations of primary hyperparathyroidism include parathyroid crisis, neonatal tetany in the offspring of mothers with parathyroid overactivity, peptic ulcer disease, and polyglandular endocrinopathy. Early recognition of these symptoms is important in avoiding a high mortality and morbidity, especially in patients with parathyroid crisis, in whom fatalities are most frequent. Using a combination of aggressive hydration, drugs, and early surgical intervention, 3 patients with parathyroid overactivity, peptic ulcer disease,

The diagnosis of the less striking complications requires clinical alertness. All the patients with these symptoms were managed by using a combined medical-surgical approach with no deaths or no complications resulting.

(The references may be seen in the original article.)

SUPRAHEPATIC ABSCESS

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Arch Surg 96(1):14-19, January 1968.*

The first successful surgical attack on a subdiaphragmatic abscess was performed by Von Volkman in 1879. The subject then remained in relative obscurity until 1908 when Barnard delivered his treatise on the surgical aspects of subphrenic abscess. In it he defined subphrenic abscess as "any localized collection of pus which is in contact with the under surface of the diaphragm."

He depicted the coronary ligaments as suspending the liver from the dome of the diaphragm and dividing the subdiaphragmatic space into six compartments. Until recently all major papers on the subject accepted this anatomical division and defined the subphrenic space as that area from the diaphragm to the transverse mesocolon.

More recently, Boyd, Moore, and Carter and Brewer have stressed the fact that the coronary ligaments suspend the liver from the posterior abdominal wall. As have a few others in the past, they state that a true subdiaphragmatic abscess must be above the dome of the liver and in direct contact with the diaphragm. There are only two subdiaphragmatic spaces, one on the right and one on the left. The interior spaces of Barnard are all below the posteriorly situated coronary ligaments and are therefore subhepatic.

The distinction is important, for the suprahepatic abscess is primarily a thoracic entity and its signs both physical and radiographic will be intrathoracic. It is important for treatment also because the suprahepatic abscess is most easily and efficiently drained by the transthoracic route while a subhepatic abscess is best drained abdominally.

Because of recent experience with the devastating results of a number of suprahepatic abscesses the following investigation was carried out.

Clinical Material

The case records of the Strong Memorial Hospital from its inception in 1926 to 1965 were reviewed. Those charts with a diagnosis of subdiaphragmatic or subhepatic abscess were investigated. Only those patients with an abscess in direct contact with the diaphragm proved at surgery or at autopsy were included in the study.

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The cases are divided into four decades in order to compare the incidence and efficacy of treatment with particular reference to the preantibiotic and postantibiotic eras.

Incidence.—In the 40-year period investigated, there have been 82 cases which meet the criteria established. There were 14 in the first decade, 26 in the second, 16 in the third, and 26 in the fourth. The relative incidence per number of general surgical procedures during that period declined in the third decade with the advent of widespread use of antibiotics. The incidence then rose again in the fourth decade, possibly due to resistance of some organisms or possibly due to the introduction of abdominal trauma as a causative factor.

Men predominated to a slight degree in all decades except the fourth where the ratio was more overwhelming, 81 percent men to 19 percent women. The overall ratio was 66 percent men to 34 percent women.

The age range was 5 to 84 years. The median age was remarkably similar in each decade and the overall median age was 55 years.

In each decade the site of the abscess was predominantly on the right side as has been found in most series. The explanation is evident from the listing of the primary causative factors which follows (Table 1).

Primary Disease.—In every decade the primary disease was related most often to the biliary system, or upper gastrointestinal tract. The total for the 40-year span was 32 percent related to the upper gastrointestinal tract and 32 percent to the biliary tract. There has been a declining incidence over the years of primary disease related to the lower gastrointestinal tract. This is consistent with the effect of antibiotics in blunting the former devastating effects of ruptured appendix. Of interest is the appearance of cases in the fourth decade that are related to trauma. Most were due to closed abdominal trauma sustained in high velocity motor vehicle accidents. The injuries were lacerations of the liver or bowel disruptions where exploration was delayed due to the closed nature of the trauma (Table 2).

TABLE 1.—Primary Causative Factors

	1926-1935	1936-1945	1946-1955	1956-1965	Total
Incidence	14	26	16	26	82
General Surgical Procedures		20,990	25,888	27,359	
Ratio		1:808	1:1618		
Sex					
Men	57%	62%	56%	81%	86%
Women	43%	38%	44%	19%	34%
Age					
Range	5-80	7-67	27-82	15-84	5-84
Median	53	52	57	56	55
Site					
Right	93%	77%	75%	62%	75%
Left	7%	23%	19%	38%	24%
Bilateral			6%		1%

TABLE 2.—Primary Disease

	1926-1935	1936-1945	1946-1955	1956-1965	Total
Upper GI * tract	14%	23%	37%	46%	32%
Biliary and pancreatic	36%	42%	32%	19%	32%
Lower GI tract, including appendicitis	43%	26%	18%	12%	23%
Trauma	0%	0%	0%	23%	7%
Other	7%	9%	13%	0%	6%

* Gastrointestinal.

Preceding Surgery.—Those patients who had preceding surgery ranged from 50 percent in the first decade to a high of 77 percent in the second. The average was 67 percent. In the first decade all patients operated on were drained and in the third only 19 percent were drained. The average number

drained was 38 percent. Coverage with prophylactic antibiotics went from zero in the first decade to 59 percent in the fourth. The overall percentage of patients receiving antibiotics at preceding surgery was 31 percent (Table 3).

TABLE 3.—Percent Undergoing Previous Surgery

	1926-1935	1936-1945	1946-1955	1956-1965	Total
Previous surgery	50%	77%	70%	65%	67%
Drain	100%	35%	19%	29%	38%
Prophylactic antibiotics	0%	10%	25%	59%	31%

Diagnosis

Symptoms.—Ninety-four percent of the patients presented with pain in the abdomen, most often at the lower costal margin. Chest pain, shoulder pain, and dyspnea, evidence of an intrathoracic problem

were far more common than signs of an intra-abdominal condition which were seen in only 9 percent. Production of foul sputum, evidence of rupture of the abscess through the diaphragm, was rare, being encountered in only 4 percent (Table 4).

TABLE 4.—Symptoms

	1926-1935	1936-1945	1946-1955	1956-1965	Total
Chest pain	72%	62%	75%	42%	59%
Abdominal pain	100%	96%	88%	92%	94%
Shoulder pain	43%	39%	44%	28%	37%
Weight loss	65%	54%	81%	50%	59%
Dyspnea	43%	12%	19%	31%	24%
Nausea and vomiting	7%	9%	13%	9%	9%
Production of foul sputum	7%	0%	6%	4%	4%
Back pain	0%	0%	0%	4%	1%

Signs.—Fever was present in 97 percent. This was usually a spiking variation in temperature. Tenderness in the abdomen particularly at the costal margins was present in 80 percent. Evidence of

pulmonary involvement by either dullness or rales was seen in 72 percent. Absence of bowel sounds was seen in 9 percent and jaundice was evident in 9 percent (Table 5).

TABLE 5.—Signs

	1926-1935	1936-1945	1946-1955	1956-1965	Total
Fever	100%	96%	100%	96%	97%
Tender abdomen	100	65	94	73	80%
Dullness or rales	72	73	62	77	72%
Absent bowel sounds	7	9	9	9	9%
Jaundice	14	19	0	0	9%
Abdominal mass	0	0	4	12	5%
Anemia	0	0	0	4	1%

Radiology.—As expected the radiographic signs were chiefly thoracic. The earliest and most common radiographic sign of a suprahepatic abscess was a pleural effusion and this was seen in 73 percent. Of these, 57 percent were tapped and all were sterile transudates except three which grew out *Escherichia coli*. An elevated diaphragm was seen in 69 percent and this was described as immobile in 34 percent. Eighteen percent had paralytic ileus and a similar percentage had lower lobe infiltrate or atelectasis. Displacement of abdominal viscera was seen in 5 percent and an upper-quadrant soft tissue mass was seen in only 1 percent. These figures were similar for the four decades (Table 6).

TABLE 6.—Roentgenographic Findings

	%
Pleural effusion	73
Elevated diaphragm	69
Immobile diaphragm	34
Air-fluid level beneath diaphragm	34
Ileus	18
Lower lobe atelectasis or infiltrate	18
Displacement of viscera	5
Right upper quadrant mass	1

Leukocytosis.—An extremely high white blood cell count (WBC) was not the rule. A WBC of 10,000 to 20,000/cu mm was recorded in 53 per-

cent, while 23 percent had an elevation greater than 25,000/cu mm, and 12 percent less than 10,000/cu mm (Table 7).

TABLE 7.—Leukocytosis

	%
>25,000	23
>20,000	12
>15,000	31
>10,000	22
<10,000	12

Surgery

Patients Undergoing Drainage.—Seventy percent of the patients underwent surgical drainage and of these, 17 percent required drainage more than once.

Technique.—Transperitoneal drainage was the route most frequently employed, being used in 42 percent. Twenty-six percent were drained by the posterior extraperitoneal approach and 7 percent anterior extraperitoneally. The transthoracic route was employed in 25 percent. This is the route advocated by Boyd and Moore who point out that the suprahepatic abscess is an intrathoracic entity. In this series it was used most often in the first decade and not at all in the most recent 10-year period (Table 8).

TABLE 8.—Technique

	1926-1935	1936-1945	1946-1955	1956-1965	Total
Transperitoneal	18%	37%	46%	62%	42%
Extraperitoneal					
Anterior	18	5	...	6	7%
Posterior	18	26	27	32	26%
Transthoracic	46	2	27	...	25%

Organism.—Sixty-six of the 82 patients, or 81 percent, had cultures recorded. Over the 40 years the organisms have remained remarkably the same and surprisingly there has been a decreasing incidence of *Staphylococcus aureus*. *E coli* and *Staphylococcus* and *Streptococcus* accounted for most of the infections. Some of the abscesses contained multiple organisms which explains the high total

number of organisms (Table 9). Fourteen percent had no growth.

Mortality

Over the 40-year span the mortality has decreased only 15 percent, from 50 percent to 35 percent. The overall mortality was 43 percent.

TABLE 9.—Organism

	1926-1935	1936-1945	1946-1955	1956-1965	Total	
					No.	%
<i>E coli</i>	4	3	4	5	16	24
Nonhemolytic <i>Streptococcus</i>	...	5	3	1	9	14
<i>Staph aureus</i>	4	3	1	2	10	15
<i>Staph albus</i>	1	5	6	10
Hemolytic <i>Streptococcus</i>	1	2	1	...	4	6
<i>Strep viridans</i>	2	1	2	...	5	8
<i>Proteus</i>	...	2	1	2	5	8
<i>Aerobacter</i>	...	1	...	2	3	5
<i>Clostridium welchii</i>	1	1	1	...	3	5
<i>Klebsiella</i>	3	3	5
<i>Pseudomonas</i>	...	1	...	1	2	3
Anaerobic <i>Streptococcus</i>	...	1	...	1	2	3
No growth	3	2	1	3	9	14
No culture available	1	8	2	5	16	24

Factors Affecting Mortality

Primary Disease.—Throughout all four decades the mortality was highest in those patients with carcinoma. Nine of 13 or 70 percent of these patients died. The mortality in patients with a perforated viscus has decreased from 50 percent to 16 percent over the 40-year period—obviously assisted by the advent of antibiotics. The overall mortality for this group was 39 percent.

To the contrary, the mortality secondary to primary inflammatory disease has not changed during this span and in the group 11 of 24 or 46 percent of the patients died. Only one of the six patients with an abscess secondary to trauma died.

Previous Surgery.—Fifty-five patients underwent previous surgery, 32 on an emergency basis, and 23 electively. The overall mortality for this group was 51 percent. The mortality for the elective group was 61 percent and for the emergency group it was 44 percent.

Type of Treatment.—Thirty-two patients were treated with drainage alone and the mortality was 28 percent. There were no deaths in the past 20 years with drainage alone.

Two of 25 patients treated with both antibiotics and drainage died with a mortality of 8 percent.

There was only one survivor in the group of 16 patients treated with antibiotics alone with a mortality of 94 percent.

TABLE 10.—Mortality and Influencing Factors

	1926-1935	1936-1945	1946-1955	1956-65	Total	Mortality
Total mortality	50%	50%	38%	35%	82	43%
Primary disease						
Perforated viscus	50	50	28	18	31	39%
Primary inflammation	33	45	50	50	24	46%
Carcinoma	100	100	66	50	13	70%
Trauma	18	6	16%
Other	100	25	0	...	8	20%
Previous surgery						
Emergency	66	45	0	50	32	44%
Elective	100	66	50	40	23	61%
No surgery	28	33	60	0	27	26%
Type of treatment						
Drainage alone	38	33	0	0	32	28%
Drainage and antibiotics	...	25	14	0	25	8%
Antibiotics alone	...	100	100	90	16	94%
No treatment	100	100	9	100%

Nine patients had suprahepatic abscess found at autopsy. In none of these was the diagnosis suspected and none had been receiving antibiotics. There have been no patients in the past 20 years who have had neither antibiotics nor drainage (Table 10).

Comment

The incidence of suprahepatic abscess after de-

creasing with the onset of antibiotics has again almost reached the preantibiotic level. In the present series the incidence of *S aureus* as the etiologic agent has decreased. Prophylactic antibiotics have not decreased the incidence.

Over the 40-year span the diagnosis was established by routine roentgenograms and fluoroscopy in most cases. In spite of the advances in medical

technology it has only been in recent years that liver scan, combined lung-liver scan, and pneumogastrogram have been introduced to aid in the diagnosis. None of these procedures was used in the present series. Gerwig and Blades state that air under the diaphragm is the most important diagnostic clue. They feel that when the potential subphrenic space is converted into an actual space by air there is an increased possibility of development of an abscess. Bondi and Erickson point out that Hoover's sign—unilateral widening of the angle between the chondral arch and the sternum—is another valuable diagnostic aid.

It would appear that the clue to earlier diagnosis is the correct interpretation of the early appearing thoracic signs. Newer diagnostic methods may then aid in more exact localization.

The technique of drainage is controversial. In view of the anatomical descriptions of Boyd, the transthoracic route seems the most logical. If the pleural space is not obliterated by inflammation, the diaphragm may be sutured to the chest wall or to the skin. Moore adds that the pleura is resistant to infection provided the lung is expanded. Certainly their results should allay the fears of those like Faxon who claims the thoracic route increases the chance of soilage.

Boyd intimates that the posterior approach advocated by Ochsner and Graves actually drains only the subhepatic space. However, the coronary ligaments do not extend far laterally from the midline, and it has been demonstrated on a number of autopsy specimens that if one goes through the 12th rib and then advances his hand cephalad along the posterior

axillary line, the suprahepatic space can be reached and drained by an extraserous route. Whipple advocated a similar approach, going through the tenth rib in the mid axillary line and then pushing the pleura upward.

In 1908, Barnard reported a mortality of 47.4 percent. In the large series prior to the antibiotic era the mortality varies from 33 percent to 47 percent. In later series of at least 30 patients, the lowest mortality reported is 16.6 percent and it ranges to a high of 43 percent. The high mortality, even when drainage is undertaken, has prompted Wetterfors to advocate treating these abscesses conservatively with antibiotics first and then drainage if they do not heal.

The present series also shows that there has been a continued high mortality for suprahepatic abscesses over the past 40 years. It has been shown that any form of treatment other than surgical drainage carries a mortality of over 90 percent. The mortality is directly proportional to the length of time between the onset of symptoms and drainage. The clue to improving the mortality figures is earlier and more efficient drainage.

Summary

The incidence and efficacy of treatment of suprahepatic abscesses over a 40-year period are reviewed. The advent of antibiotics has done little to decrease the incidence and mortality. The key to an increased survival remains early, efficient surgical drainage.

(The references may be seen in the original article.)

MEDICAL ABSTRACTS

ACID-BASE DISTURBANCES IN 50 SEVERELY WOUNDED PATIENTS IN HEMORRHAGIC SHOCK PRIOR TO TREATMENT

LT C. T. Cloutier, MC USN, LT B. D. Lowery, MC USNR, and LCDR L. C. Carey, MC USNR.

Evidence obtained in animal shock models indicates that the initial acid-base disturbances in hemorrhagic shock is that of metabolic acidosis. Fifty severely wounded, previously healthy, combat Ma-

rines in hemorrhagic shock had arterial blood samples drawn prior to resuscitation.

The mean evacuation time from wounding to hospitalization was 94 minutes. None had received any intravenous therapy prior to admission. On admission the mean arterial blood gas values were; pH 7.38, pCO₂ 35 mm Hg, HCO₃ 22.7 mEq/L, total CO₂ 23.4 m Mol/l and hemoglobin 11.5 grams %. Using the acid-base alignment normogram according to Siggaard Anderson, 35 patients demonstrated a base deficit, 11 a base excess, with the means

being (-) 6.39 mEq/L and (+) 5/45 mEq/L respectively.

Thirteen patients were acidotic with pH less than 7.31. An additional 10 patients had normal pH values but a base deficit of 3 mEq/L or more. They were considered to represent compensated metabolic acidosis. Ten patients were frankly alkalotic with pH above 7.48. Of these, 7 demonstrated uncompensated respiratory alkalosis. There were 15 patients whose acid-base pattern was normal on admission.

No correlation could be found between the acid-base disturbance and either the time elapsed from injury to admission or the types of wounds.

These studies point out the necessity of careful acid-base evaluation prior to instituting correctional therapy.

(From: The Naval Medical Research Institute, Experimental Surgery Division, National Naval Medical Center, Bethesda, Maryland 20014, The Station Hospital, U.S. Naval Support Activity, DaNang, Republic of Vietnam, and the Naval Medical Research Unit-II, Taipei, Taiwan.)

EFFECT OF EXOGENOUS LACTATE ON ARTERIAL LACTATE LEVELS IN HUMANS IN SHOCK

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MC USN, and LCDR L. C. Carey, MC USNR.*

The effect of large volumes of exogenous lactate has been shown to lower the arterial lactate levels in experimental animals in shock. The effect on humans is less clear. Twenty-four severely wounded battle casualties have been studied. All were in shock and 18 had blood pressure of less than 80 mm Hg on admission. Arterial blood samples were obtained on admission before treatment, immediately after surgery, every six hours postoperatively for 24 hours and then daily for four days.

The patients were resuscitated with commercial lactated Ringer's solution and whole blood. From admission until the end of the first 24 hours postoperatively, they received an average of 5500 cc of whole blood and 11,400 cc of Ringer's solution.

The mean arterial lactate on admission was 50 mg %, (normal for the method used 5-20 mg %). At the end of surgery the mean had risen to 56 mg %. At 18 hours following surgery the average was 14.9 mg %. These data show that large exogenous lactate loads and whole blood effectively lower lactate levels in humans in shock.

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MAGNESIUM METABOLISM

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New Eng J Med 278(12):658-663, Mar 21, 1968
and 278(14):772-776, Apr 4, 1968.*

Over the decade since this subject was last reviewed in the *Journal* much has been added to the knowledge of normal human magnesium metabolism and of its alteration in disease. This has ensued largely because of the advances made in the quantitative analysis of this element in biologic samples. A major step forward has been the successful use of flame methods to measure magnesium in body fluids and tissues. Application of the technics of emission spectroscopy led to the perfection of a multichannel flame spectrometer that gave precise and accurate determinations of the relatively small amounts of magnesium in serum, urine and tissues samples. The more recent development of atomic absorption spectroscopy provides instrumentation for general use whereby multiple determinations of minute amounts of magnesium can be reliably made on small samples in a matter of minutes.

The availability of this simple, precise method has already led to a better understanding of the role of magnesium metabolism in human disease, a process that should accelerate in the next few years.

The methodologic developments of the past decade allow magnesium to be measured in body fluids and tissues with the same facility as sodium and potassium. Consequently, a precise definition of magnesium deficiency in man has ensued that is now recognized as being similar to that long known to occur in animals. Human magnesium deficiency is seen frequently in a variety of gastrointestinal and endocrine disorders. Abnormalities of magnesium metabolism are being recognized increasingly often in seizure disorders in infancy. In particular in the next few years, the measurement of the major biologic cations simultaneously will provide important knowledge of the complex interrelationships between electrolytes. It can be anticipated that considerable understanding of the effects of altered magnesium metabolism on the intracellular, biochemical functions of magnesium will be forthcoming.

SURGERY OF THE ESOPHAGUS

*E. W. Wilkins, Jr., MD, and D. B. Skinner, MD,
New Eng J Med 278(16):887-891,
Apr 18, 1968.*

No previous Medical Progress report has been limited exclusively to surgery of the esophagus. The topic was included most recently in a review of the broad field of thoracic surgery by Scannell and

Wilkins in 1960. The concurrent availability of new information on esophageal anatomy and physiology derived from modern recording devices and the fruition of long-term analyses of the results of treatment have together led to renewed enthusiasm for a more rational surgical approach to esophageal disease. More than 1,000 articles have in fact been published in the English-language literature during the past five years.

DENTAL SECTION

STUDY OF HISTOLOGIC REPAIR RESPONSES FOLLOWING OSSEOUS- DENTAL TRANSPLANTATION

*A. B. Luke and P. J. Boyne,
NMRI, Bethesda, Md.*

This study was undertaken to observe the repair responses following autogenous orthotopic transplantation of a block section containing a fully formed tooth together with surrounding osseous tissue. In 16 adult dogs a mucoperiosteal flap was raised and the maxillary 1st premolar was removed bilaterally together with 5 mm of surrounding alveolar bone on all surfaces. These sections were then transplanted to the contralateral side and stabilized by means of intraosseous wire ligatures. In addition, in the same animals the mandibular 3rd molars were extracted without the concomitant removal of surrounding bone and transplanted contralaterally. Tetracycline was administered at selected postoperative intervals. Excised biopsies of the "osseous-dental" and control transplants were obtained at 1½, 2, 3, 8 and 10 months. Twenty-four teeth in 32 osseous-dental transplants were completely exfoliated before the 6th post-surgical week. Eight of the transplanted mandibular 3rd molars

were likewise lost to followup. Tetracycline induced fluorescence revealed a marked, progressive root resorption of the teeth contained in the osseous-dental block. Excellent union of the osseous portion of the graft to the host bone was evident by the 2nd post-surgical month. Remodeling of the bone of the graft continued throughout the later postoperative stages. One of the osseous-dental transplants and five of the transplanted mandibular teeth exhibited only minor resorption. These observations indicate that the alveolar bone surrounding the tooth-bone grafts in this study did not mitigate the progressive resorption of the transplanted teeth.

Supported by NMRI Research Project MR005. 19.6037.

The assertions and opinions contained herein are those of the authors and are not to be construed as reflecting the views of the Navy Department or the naval service at large.

The experiments reported herein were conducted according to the principles enunciated in "Guide for Laboratory Animal Facilities and Care" prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

(Abstracted by: CAPT P. J. Boyne, DC USN.)

PERSONNEL AND PROFESSIONAL NOTES

ADVANCED DATE SET FOR ASSIGNMENTS TO TRAINING IN CIVILIAN INSTITUTIONS

With the passing of each year, those officers selected for advanced training in civilian institutions

are encountering increased difficulty in obtaining admission largely because of the late receipt of their applications by the civilian school. The basis of the problem stems from the date set for the receipt of

such applications by the civilian universities which is generally by November prior to the start of the following academic year.

In an endeavor to provide an earlier notification to those officers selected for *advanced training in civilian institutions*, the Dental Training Committee will meet in the Bureau of Medicine and Surgery in early October. It should be stressed that this meeting is but one of several held throughout the year. The prime purpose of the October meeting will be to select, in advance of the regular January meeting, as many of those officers as is possible who desire to attend *civilian institutions* during the ensuing year. It is expected that additional officers will be selected for such training at subsequent meetings. However, every effort will be extended toward the early selection and consequent early notification.

It should be emphasized that this projected plan applies only to those officers desiring to attend civilian institutions. Applications for other training will be processed as set forth in MANMED, Chapter 6, Section 16.

In order to accomplish the above proposal, applications for advanced training at civilian universities must be forwarded so as to be received in the Bureau of Medicine and Surgery not later than 1 September in order that processing may be effected for consideration at the October meeting.

MANMED will be changed at a later date to reflect the above proposal.

NAVAL DENTAL CLINIC, LONG BEACH, CALIFORNIA, UTILIZES WESTCOASTER HAULMASTER SCOOTER TO PROVIDE DENTAL REPAIR SERVICE

The Naval Dental Clinic, Long Beach, California, utilizes a Westcoaster Haulmaster scooter type truck, Model No. 762, to render dental repair service. According to the Commanding Officer of the Naval Dental Clinic, the truck has proved to be a most valuable means of transporting dental repair tools and equipment directly to dockside locations of ships requiring this type of service. Due to its relatively small size (1 passenger, 800 lbs. capacity, 116" long, 59" wide, 72" high), parking alongside ships at piers is permissible in contradistinction to conventional size trucks or automobiles. Additionally, with its portability and conveyance capabilities, a substantial saving of time has resulted in rendering complete dental repair services to ships and the two dental buildings of that command.

Other naval dental activities which supply dental repair services to ships and outlying clinics may wish to consider the possibility of obtaining a similar type vehicle. Information on the vehicle utilized at the Long Beach Dental Clinic may be obtained from: Commanding Officer, Naval Dental Clinic, Naval Base Los Angeles, Long Beach, California 90801.

NEW CORRESPONDENCE COURSE

Naval Dental School, National Naval Medical Center, Bethesda, Maryland.—The Naval Dental School announces a new correspondence course for dental officers, *Special Oral Surgical Procedures and Fractures*, NavPers 10516. This course and the concurrent one, *General Oral Surgical Procedures and Exodontia*, NavPers 10729-A, replace the course *Oral Surgery*, NavPers 10729, published in 1960. Both courses are based on G. O. Kruger's *Textbook of Oral Surgery*, 2nd edition.

The subject matter of the text has been divided into two courses to meet more directly the needs of dental officers according to their types of practice and experience.

The new course has five assignments, which cover the principles of surgery and surgical technique; salivary glands and ducts; the temporomandibular joint; cysts of the bone and soft tissues of the oral cavity and contiguous structures; surgical aspects of oral tumors; fractures; and defects, deformities, and other considerations.

AMERICAN BOARD OF PERIODONTOLOGY

At the recent meeting of the American Board of Periodontology, several changes were made which will be of interest and aid to prospective candidates. Basically, the changes are that an individual can take his written examination upon completion of his two-year formal graduate education program. The time of this examination will always be announced and it appears that it may be given each year prior to the American Academy of Periodontology fall meeting. The first such examination will be given in Hollywood, Florida, at the Diplomat Hotel on Tuesday, October 22, 1968. Case reports that are submitted hereafter must be satisfactory before the candidate is permitted to take the oral-clinical examination.

(Information provided by: Dr. Henry M. Swenson, Secretary-Treasurer, American Board of Periodontology.)

NURSE CORPS SECTION

THE ROLE OF THE CLINICAL SPECIALIST IN NURSING

Helen Shields, RN MS.

The Role of the Clinical Specialist in Nursing was presented by Helen Shields at a recent nursing in-service education meeting at the Naval Hospital, Charleston, South Carolina. The author is a clinical specialist in cardiovascular disease at Georgetown University, Washington, D.C.

When considering the sociological changes in the professions one is struck by many facets. These range from population growth, urbanization, impact of wars, growth of scientific knowledge, impetus to increased education for the population, and changes in organization structure. Bureaucracy, technocracy, and socialization are growing trends producing a great impact on the professions and necessitating considerable reflection on the future of all working people.

The nursing profession is and has been climbing the ladder towards true professionalism. The clinical specialist is the newest entity and is now under much evaluation in order to interpret the growth and direction she is to follow.

What are some of the indirect causes for the development. The expansion of the field of education has placed more emphasis on collegiate education for all people. Also the increase in the number of women in the working population has encouraged young women to seek careers. Combine a feminine career with higher education and the field must broaden. Also the field will diversify and hence the need for specialization. Another factor contributing to this is, I feel, the need for the nurse to give very personal concentrated care to selected patients. This is frequently done only by the private duty nurse or a staff nurse who is assigned a critical patient in lieu of a private duty nurse. The level of frustration felt by some staff nurses at not being able to devote the time and attention to ill patients is also a driving force towards specialization. If the decision is made to specialize, what then is the next step? Some pursue the course of specialization through experience. That is to say that they associate themselves in a certain defined area of knowledge and give care to just those patients without seeking depth of knowledge in the field. She usually develops her skills and knowledge on an empirical basis. Most frequently these nurses reach a high level of expertise but are

narrowly defined. The more professional approach to specialization is that which is developing today.

A young woman emerges from the required years of schooling with a broad base of superficial knowledge. In choosing her academic site for higher education she should select a university which has a curriculum encompassing the social and basic sciences in order to give stronger footing to her development as an individual who will be living and working in a rapidly dynamic society.

It is during the clinical experience curriculum that the student will develop an interest in a specific area. From this point onward she will tend to develop her desire to know more about a certain area and should be encouraged to seek graduate education in that area. How much clinical experience is needed before graduate school? That is an area which needs to be considered. Self confidence in one's own skills and a feeling of responsibility towards one's chosen field take time to develop. Whether this should come before graduate school or wait until later should be thoughtfully considered for each student and by each professor and/or employer. A year's structured internship for Baccalaureate graduates is being tried by some and thought of by others at the Master's level. This is a time for what I call the shakedown cruise. All the parts are there but can they function!

The Master's programs now available in the clinical areas are very few. Maternal and child health, psychiatry, cardiovascular disease, and neurology are the ones I am familiar with. The broad area of Medical and Surgical nursing does not seem to be a specialization but an attempt to upgrade generalized nursing. The programs for administration and education are out of the field of clinical nursing. The curriculum of a specialized clinical area should cover the broad base of all it connotes. The nurse should be familiar with Public Health aspects, research in the field, etiology and demographic aspects, diagnosis and therapy, plus all the psychosocial impacts. Her skills of teaching are an area to be developed as she will be a resource person for everyone.

This brings us to the function of the clinical specialist. That this is a field for pioneers is all too true and no real job description has as yet been

adapted for all the areas. I rather doubt that one job description will cover each individual's approach to her job. We all have strong points of interest and inherent talents which we will develop in our own way. This then sets the first functions—to function independently and outside the administration-supervisor authority ladder. The ability to do this is a hoped-for product of education and experience in a responsible person. This also infers that the specialist is not in a position of authority herself and does not have the function of hiring, firing, or disciplining personnel. This also infers that she has access to patients in whatever location she may find them in the hospital compound. She is not restricted geographically but only by her specialty. The removal of authority poses problems: to whom does the nurse report and who is responsible for evaluating the performance of the specialist? These are as yet unanswered questions. The services that the clinical specialist offers the patients and the staff range from direct patient care of complex nursing situations to the didactic classroom teaching of nursing service personnel. In between are cooperative planning of care for specific patients, acting as resource person for unit conferences, liaison between nursing and other departments as they affect a specific patient situation, incidental instruction wherever and whenever necessary. The responsible, knowledgeable person will seek all avenues of strengthening patient care both in the hospital and through participation in community activities. Membership in professional organizations is necessary for the exchange of ideas, development of new concepts and testing theories. Attendance at work shops, seminars, journal clubs, conferences, and formal classes all continue the education of the clinical specialist. Her responsibility in this area is great in that she must progress and assist others to absorb some of her knowledge.

Publication and actual participation in programs is her best outlet for a broader population. That is not to say that she must publish or perish, but the whole should benefit from the part.

As to the specifics of what a clinical specialist can do, let us look at one area—transfer of a patient from one unit to another. We are generally agreed that this is a rough spot for all concerned. The unit that gives up the patient usually loses contact with

him. The unit receiving the patient usually has scanty information about the preceding events. The patient is caught between what has been and what will be his care planning. There should be good preparation of the patient for transfer. This is accomplished through explanation of the stages of his physical progress and the needs he has for those changes. Personal contact with a member of the receiving area should be possible prior to transfer. A written evaluation of the patient and his particular areas of concern is the responsibility of the transferring unit. A verbal review with the receiving staff is in order to be followed the next day by a unit conference as well as personal observation by the transferring unit.

The follow-through on this patient will be complex because he is an out-of-town referral. However, it could be possible to send a resume to the patient's home town physician's nurse so she could gain some insight into the therapy and difficulties the patient might experience. I will have to work this idea out and see how it is best to be handled.

An area of big concern is how to evaluate the patient in order to determine his needs. Many of us use no formula or format that gives real guidance. Hence it is rather haphazard and may benefit only that one patient but value is lost in that it can in no way contribute to an organized body of knowledge or aid in the accumulation of ways and means to approach similar problems.

One of the best discussions of this is in a new publication that is the result of several years of effort by the Western Interstate Commission for Higher Education published in 1967. I heartily recommend it for real scrutiny.

The core of the scheme is the definition of the nursing process. This is considered to be composed of five elements—perception, communication, interpretation, nursing intervention, and evaluation.

The manner in which the nurse approaches the evaluation of the patient's needs was explored in several different formats each of which has its own appeal. These are changes in body image and alteration of body function.

One of these—alteration in body function—seems to me to be very usable. The outline for this process is as follows.

Content or Guide for Study of Content

<u>Alterations</u>	<u>Manifestations</u>	<u>Knowledge Basic to Nursing</u>
Nature of alteration of physiological function and psychological function.	The effect of the alteration in terms of signs, symptoms, results of examinations, changes in behavior, attitude.	Knowledge from natural, social, medical, and nursing sciences which applies to understanding of the alterations and/or what can be done for the alterations.
<u>Nursing Knowledge</u>	<u>Guide to Action</u>	
Propositions synthesized from natural, social, medical, and nursing sciences, as identified in Col. I, II, III, which provide rationale for nursing action.	Specific directions for action of the nurse to alleviate the patient's discomfort.	

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PREVENTIVE MEDICINE SECTION

CHOLERA

The Bulletin of the World Health Organization, Vol 37, No. 5, 1967, devotes its entire issue of 120 pages to the results of many studies conducted by the Joint Philippines-Japan-WHO Cholera Committee during 1964 and 1965. Among the topics discussed are: laboratory and field trials of various cholera vaccines, carrier studies and therapy.

This single number of the Bulletin may be purchased for \$2.25 from the Columbia University Press, 136 South Broadway, Irvington-on-Hudson, New York 10533. An annual subscription (12 numbers) to the Bulletin costs \$25.00.

THE GREEN MONKEY DISEASE EPISODE—1967

USDHEW PHS CDC Vet Public Health Notes
pp 2-3, Mar 1968.

Late in July 1967, 4 shipments of African green monkeys (*Cercopithecus aethiops*) from Uganda arrived in West Germany. Most of the animals were destined for two companies—the Behringwerke AG in Marburg and the Paul Ehrlich Institute in Frankfurt—where their kidneys were to be used in the manufacture of vaccines.

By early September, 20 employees at Behringwerke and 4 at Ehrlich Institute became ill with "green monkey disease." Four other persons—doctors and other medical workers who cared for the employees—also became ill; 7 employees died.

Most of the victims had taken part in nephrectomies on the monkeys to obtain kidney tissue for use in cell cultures. Others had come in contact with tissue cultures.

Initial symptoms of the disease included severe prostration, nausea, vomiting, diarrhea, and muscle ache. Other symptoms were conjunctivitis, rash, changes in white cell counts, and bleeding from mucous membranes. There was also involvement of the liver, heart, and brain. Deaths usually occurred 7 to 12 days after onset of illness; fatality rate was 25%.

On September 1, 1967, the National Communicable Disease Center (NCDC) Atlanta, Georgia was invited by the German Ministry of Health to send observers to study the outbreak. James W. Mosley, M.D., chief of the Epidemiology and Research Analysis Section, and John H. Richardson, D.V.M., chief veterinarian, Domestic Operations Section Foreign Quarantine Program visited the laboratories at Frankfurt and studied the patients. NCDC's concern was valid. An estimated 12,000 green monkeys enter the United States each year and are used primarily for vaccine production.

After the complete clinical picture had unfolded, all observers agreed that the disease represented a new disease entity. Although green monkey disease resembles some of the hemorrhagic fevers, it corresponds to none in all respects. A wide variety of treatments seemed to have no effect on the disease.

Uganda stopped exporting green monkeys, pending further investigation. At the National Institutes of

A shigellosis outbreak, associated with bottled pasteurized milk, occurred in November 1967. These recent episodes may be indicators that more of a food-borne *Shigella* problem exists than is realized. Again, a paucity of data to evaluate laboratory procedures for recovery and isolation of shigellae from foods is a handicap.

Viral Food-Borne Illness

There are over 100 different viruses which thrive in the human intestinal tract. The incidence of food-associated hepatitis outbreaks has increased in the past 2 years. These have been reported from various parts of the country and have implicated a variety of foods. Unfortunately, investigators are hampered by the inadequacy of present laboratory techniques for isolation and recovery, however, the spread of the virus through food and water has been demonstrated epidemiologically.

More Sanitation Needed

Effective control of the food-borne illnesses, whether they be bacterial or viral in nature, entails a much higher and more rigid level of sanitation than generally has been practiced, or required by industry or by health and regulatory officials. Studies in milk drying plants have demonstrated the significance of control and proper use of air and air systems in food processing. Presently, study is being made into the role of airborne microbial contamination, especially in dusts, fogs, and other aerosols that may be created during the processing.

The importance and influence of plant environmental conditions; personal hygiene and sanitary practices of employees; separation of raw material and finished goods processing areas; and proper maintenance of equipment, including proper design to permit adequate cleaning, have been manifested repeatedly.

Today's mode of living and technology probably renders the population more susceptible to food-borne infection. The convenience foods, ready-to-eat items, and frozen prepared dinners requiring only minimum heating prior to serving open avenues for mass infection. Production and distribution system is such that today the output of a plant may be distributed nationwide, or even worldwide. This means that an infected employee, or a breakdown or deterioration of some phase of plant sanitation, can infect thousands of consumers instead of a limited surrounding community. The population concentration, human and food animal, with the resultant

waste disposal and pollution problems, is likewise conducive to spread of infection.

While sanitation is basically and fundamentally a preventive science, efforts are being made to trace and determine the factors responsible for bacterial contamination. One must give more study and consideration to assure that contamination *does not* occur. Before this goal can be fully attained, however, there is need to develop more sound scientific knowledge upon which meaningful control programs can be based. Microbiological methods must be developed, refined, and made more specific and sensitive.

The National Academy of Sciences is undertaking a broad study of *Salmonella* and its impact on human health, food technology, and animal agriculture in the United States. The project will be carried out under the joint sponsorship of the U.S. Department of Agriculture and the Food and Drug Administration. The project will include a survey of the problem on contamination in the food and agricultural industries by salmonellae, the chain of events that leads to outbreaks of salmonellosis in man, and the effectiveness of current control methods.

CONSEQUENCES OF NATURAL EXPOSURE TO RUBELLA DURING PREGNANCY

G. C. Brown, *Proc Soc Exp Biol Med*
127(1):340-344, Jan 1968.

Blood specimens collected early in pregnancy and again at delivery from 347 women with histories of exposure to rubella were tested for antibodies by the indirect fluorescent-antibody technique.

Gamma globulin had been administered to 72 following exposure. Previous immunity was detected in 265 of the women who were found to have antibodies of identical titer in both specimens.

Serological evidence of infection during pregnancy was demonstrated in 41 of the 82 women whose first sera were negative for antibodies. Of these infections, 26 were subclinical and only 15 were recognized as clinical rubella.

Gamma globulin did not reduce the incidence of infection in susceptible women, which was actually higher than in the uninjected, but markedly suppressed the development of clinical disease. Damage to the fetus following first trimester infection occurred only once among 14 pregnancies in which gamma globulin had been administered. By contrast, 4 of 27 pregnancies of uninoculated women terminated abnormally, even though 20 of them were infected after the first trimester.

There was evidence of delayed infection following injection of gamma globulin and the possible significance of this phenomenon is discussed.

HUMAN BRUCELLOSIS—UNITED STATES, 1967

USDHEW PHS CDC Vet Public Health Notes, pp 3-4, Apr 1968.

In 1967, a total of 248 cases of human brucellosis in 35 states were reported to the NCDC, Atlanta, Georgia. This is the lowest total since 1947—the year of highest incidence of human brucellosis. Iowa reported the most cases, 35, followed by Virginia—29, Texas—27, and California—21. Most cases were reported in June 1967; only 12 cases were reported in February.

Brucellosis surveillance reports were received by the Zoonoses Surveillance Unit, NCDC, on 207 of the 248 cases. Fifty-two percent (107) of the 207 cases occurred in packinghouse workers. The num-

ber of cases in this group was higher in 1967 than in either 1965, when 89 cases were reported, or in 1966, when 93 cases were recorded. Probable sources of infection for the packinghouse workers included 51 exposed to swine, 34 exposed to cattle and swine, 14 exposed to cattle, 1 exposed to goats or sheep, and seven with unknown exposure.

Of the 207 cases, 24 (12%) were in farmers. Unlike packinghouse workers, whose most probable source of infection was swine, half of the farmers with brucellosis traced their illness to exposure to cattle. Only 3 of the 24 farmers gave histories of contact with swine only.

Ten of the 207 cases (5%) were in veterinarians. Accidental exposure to strain 19 vaccine was reported in 4 instances among veterinarians.

Of 207 patients (5%), 10 had histories of ingesting raw milk.

In 1967, caribou were implicated as the probable source of brucellosis in 6 Alaskans. In the medical histories of these 6 patients, there were known instances of handling caribou carcasses or eating raw caribou meat.

KNOW YOUR WORLD

Did You Know?

That originally the 3-nautical mile limit of offshore waters had been set by the effective distance a cannonball could be fired in the days of sailing vessels?

Nations now choose a distance between 3 and 12 miles from their shores. The United States recently changed its territorial water claim from 3 to 12 miles. In the past designated territorial waters were for defense purposes; now, fishing and mineral rights are included. However, the Geneva Convention of 1958 provides for a nation the sovereignty over its continental shelf to a depth of 200 meters or to the depth of exploitation of natural resources. Several Latin American countries have made claims of exclusive rights to a distance of 200 miles from their coasts. No country owns the floor of the open ocean.¹

That for the first time in 35 years, tularemia has been discovered in the Province of Quebec?

Five cases from the counties of Beauce, Charlevoix, Rimouski had been reported to the Provincial Department of Health. Rabbits are suspected and an epidemiological investigation is in process.²

That rabies can be contracted by animals that were fed infected material?

Investigators at the CDC Atlanta are certain that there is no danger of humans getting rabies from food, but animal experiments have shown that under "ideal conditions" the disease can be transmitted by the gastric route. It has been believed that rabies could be caught only from the bite of an infected animal, or, rarely, through breathing of contaminated air. In these experiments, 8 of 30 mice died after being fed extremely large doses of the brains of rabid mice.³

That over a million persons accidentally ingest toxic substances each year and about 2,100 die?

Many more sustain permanent or crippling injuries. Since 1963, the death rate from such poisonings has remained at almost 11 per million population of 16% higher than in 1960.⁴

That from July 1961 to July 1962, of the 24,069 population of Trinidad, 23,900 (98.5%) took part in a diabetes survey and have been followed up for 5 years?

Five hundred twenty-one (2.20%) had postprandial glycosuria; 488 (1.89%) satisfied the criteria for diabetes. Of these 267 (1.13%) were known diabetics and 181 (0.76%) were unknown. While diabetes is rare under 20 years of age, the prevalence-rate is 3.45% over the age of 20. Females show a higher prevalence than males, 2.10%: 1.53%. Diabetes is more common among East Indians than Negroes, 2.37%: 1.44%.⁵

That imported foods, drugs and cosmetics worth approximately \$4 billion enter the United States annually through 293 ports of entry and 71 custom stations?

Drug importation valued at \$150 million dollars annually enters the United States. The Food and Drug Administration is charged through a program of surveillance sampling of imports to determine the admissibility in compliance with the Food, Drug and Cosmetic Act, the Tea Importation Act, and Import Milk Act, assisted by the Bureau of Customs, Department of the Treasury.

Milk and cream may be imported only by permit under the Import Milk Act, after certain sanitary and other prerequisites are fulfilled. At present 3 firms in Canada, 1 in New Zealand and 1 in Denmark hold effective permits to ship milk and cream to the United States.⁶

That since the beginning, 20 years ago of the World Health Organization activities in Southeast Asia region, nearly 500 projects were completed so far?

In India, the death rate dropped from 27 per 1,000 to 17 and infant mortality from 183 to 100. Plague has disappeared. Deaths from cholera were reduced from 87,000 to 8,300 and from Smallpox from 40,000 to 9,000. Malaria dropped from 75 million to 110,000.

During 1967, 191 projects in operation covered such subjects as malaria eradication; tuberculosis control; smallpox control and production of freeze-dried vaccine; cholera, leprosy, and communicable disease control; health laboratory services and production of vaccines; health statistics; public health laboratory administration and rural health services; maternal and child health; nursing; environmental health and water supply; education; nutrition; mental health; dental health; medical rehabilitation; radiation; quality control of drugs and medical education.⁷

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EDITOR'S SECTION

ADDENDUM TO NAMRU #3 HISTORY

CAPT J. M. Amberson, MC USN, Chief, Preventive Medicine, at the Naval Medical School, National Naval Medical Center, Bethesda, Maryland explained in a recent letter to the Editor that, although the American Typhus commission had a laboratory in Cairo, Egypt, NAMRU #3 (History on inside front cover of U.S. Navy Medical News Letter of 5 April 1968) was not a direct outgrowth of that facility.

CAPT Amberson personally submitted a proposal for a post-war medical research unit to the U.S. Minister for Lebanon and Syria in Beirut in October 1945. After a warm endorsement, it was forwarded to BUMED via the Department of State and commissioned by the Navy in 1946 as NAMRU #3.

RADIOISOTOPE ANGIOCARDIOGRAM

Scientists of the Public Health Service's National Institutes of Health have developed a new technique

that employs the radioisotope technetium-99m and a gamma scintillation camera to visualize the heart and great vessels.

The resulting "radioisotope angiocardioqram" provides diagnostic information on the anatomy and function of the heart and great vessels similar to that obtained by conventional x-ray visualization techniques, but it eliminates the adverse reactions that occasionally attend injection of radiopaque dyes required for adequate x-ray definition. When injected in large quantities, these dyes can produce nausea, slowing of the heart, and even shock.

The new method was reported in San Francisco at the 17th Annual Scientific Session of the American College of Cardiology by Drs. Dean T. Mason, Lawrence S. Cohen, and Eugene Braunwald, of the Cardiology Branch, National Heart Institute; and Drs. William L. Ashburn and John C. Harbert, of the Department of Nuclear Medicine, NIH Clinical Center.

It entails injecting a small quantity of technetium-99m via catheter into a selected heart chamber or blood vessel. The radioisotope emits gamma rays. These are detected by a gamma scintillation camera positioned over the patient's chest. The camera contains a crystal that scintillates—e.g., emits flashes of light—whenever gamma rays strike it. A television camera then records the flashes from the scintillation camera.

As the isotope traverses the heart and great vessels, its gamma emissions define anatomic details and bloodflow patterns that are highly useful in the diagnosis of congenital or acquired heart disorders. The radioisotope and angiocardigram can also be recorded on videotape and replayed for detailed analysis.

Radiation exposure to the patient is minimal. The technique requires only small quantities of technetium-99m. Moreover, the isotope is rapidly cleared as it passes through the lungs and subsequently leaves the body in the urine.

The scientists have tested the technique in patients at the time of diagnostic catheterization for a variety of congenital and acquired forms of heart disease. They reported that the radioisotope angiograms accurately reflected hemodynamic alterations resulting from these conditions.

The technique has already been used to estimate bloodflow to various organs or regions of the body. The investigators feel that it will also be useful in determining heart output (the amount of blood pumped per unit of time) and the volumes of the main pumping chambers during various phases of the heart's contraction cycle. Thus the technique may prove to have numerous applications both in cardiovascular diagnosis and in research on cardiovascular physiology.—NIH, Bethesda, Md.

THYROCALCITONIN, A NEW THYROID HORMONE

Fundamental and applied research by National Institutes of Health scientists on thyrocalcitonin, a new thyroid hormone recently discovered in several animal species, has

provided the first chemical definition of the hormone's structure that has just led to synthesis of the hormone by Swiss researchers;

provided a sensitive method of measuring the normally minute amounts of hormone circulating in the blood;

established through the assay method the hormone's physiological importance in bone and mineral metabolism; and

demonstrated that the purified hormone, administered to patients suffering from high blood calcium levels and bone demineralization, produces rapid and beneficial results.

These findings, of far-reaching scientific and medical importance and the subject of intensive research efforts by many research teams in this country and abroad, were presented on Tuesday, May 21, at the *International Symposium on Protein and Polypeptide Hormones*, Liege, Belgium, by Dr. John T. Potts, Jr., of the National Heart Institute's Laboratory of Molecular Diseases. Dr. Potts, head of the Laboratory's Section on Polypeptide Hormones, and his co-workers, Drs. Hugh D. Niall, Henry T. Keutmann, H. Bryan Brewer, Jr., Leonard J. Deftos, and Michael R. Lee, have also reported these findings in the April and May issues of the *Proceedings of the National Academy of Sciences*.

Discovery

A Canadian scientist, Dr. Harold Copp, first identified the existence of a blood calcium-lowering substance, later shown to be thyrocalcitonin, during animal studies performed in 1961. The substance was postulated to account for an otherwise inexplicably rapid rate of fall in blood calcium levels noted in certain experiments. These effects could not be explained merely by changes in levels of parathyroid hormone, the only hormone known at that time to affect blood calcium. In 1963, Dr. Paul Munson and co-workers correctly identified the thyroid gland as the origin of the new hormone. They extracted the active substance from hog thyroids, and proposed that thyrocalcitonin was a second major hormone elaborated by the thyroid gland. It was credited with acting in concert with parathyroid hormone to regulate blood calcium, and preventing calcium demineralization and attendant softening of bones.

But much work remained to be done to show that thyrocalcitonin was indeed a hormone. It was not enough to demonstrate its mere presence in animal thyroid tissue and its release in response to abnormal elevations of blood calcium. It required proof that the proposed hormone was continually released by the thyroid into the bloodstream in small amounts to perform a normal physiological role, i.e., to control the rate of bone demineralization, and thereby help to regulate blood calcium.

Much of the evidence required for this proof, with all its scientific implications and clinical promise, has been provided by the National Heart Institute studies.

The NHI scientists had previously isolated the hormone in pure form from partially purified extracts of pig thyroid. The final product had been increased in potency 50,000 times (fresh thyroid tissue contains only 5 parts per million as thyrocalcitonin) and passed stringent tests of purity. No small task in itself, this accomplishment in late 1967 paved the way for the currently reported studies of thyrocalcitonin structure, synthesis of the peptide, and development of an accurate method of assaying it in the blood. These studies were made possible by Armour Pharmaceutical Company, Kankakee, Illinois, who supplied large quantities of partially purified pig thyroid extract.

Structure

The studies that led to isolation of the pure hormone also characterized the protein nature of the substance, a peptide consisting of 32 amino acids, but provided no information about the arrangement or sequence of these amino acids in the complete thyrocalcitonin molecule. In defining the molecule's structure, the painstaking process of sequence determination was carried through to completion not once but twice, each time via a different method. Both of the methods used by Dr. Potts and co-workers employed various agents as "chemical cleavers" to cut the hormone into its component amino acids, or into both larger and smaller fragments.

In their first approach, the scientists subjected the peptide to a process of sequential degradation whereby one amino acid at a time is removed, identified and measured. The process was repeated until the order of the entire 32 amino acids had been determined. This stepwise picking-apart of the molecule is a laborious undertaking. It requires the careful control of reaction conditions to prevent undesired chemical cleavages.

In the second approach, the scientists used various enzymes and chemical reagents to cut the pure hormone into fragments. Analysis of 61 such fragments resulting from the complete breakdown of the molecule indicated only one possible order for the 32 amino acids comprising the molecule.

The identical results achieved by the combination of the two independent approaches constituted virtual proof that the correct structure of thyrocalcitonin had been deduced by the NHI group. The 32 amino

acids of the molecule are arranged in a single polypeptide chain with a large loop at one end.

Ultimate proof that the correct structure has been obtained and practical application of the knowledge of hormonal structure requires laboratory synthesis of the hormone. This has been accomplished. Within the past week, Dr. St. Guttman and co-workers at Sandoz Ltd., a pharmaceutical company in Basel, Switzerland, have achieved complete synthesis of highly active thyrocalcitonin, by using as their "blueprints" the structural information supplied by Dr. Potts' group. Ciba Pharmaceutical Co., also in Switzerland, and Lederle Laboratories in the United States, have also announced considerable success in efforts to synthesize the hormone. Thus, a synthetic product promises to become widely available for medical use. Knowledge of those portions of the structure most important for biological activity would permit synthesis of altered forms of the molecule having enhanced biological activity. (Such a product, synthetic corticotrophin, six times more active than the naturally-occurring hormone from the pituitary gland, was recently developed by Dr. Guttman's group at Sandoz.) Dr. Potts and co-workers have already identified one site in the thyrocalcitonin molecule, an amino acid whose extensive alteration does not affect the molecule's hormonal activity, that may lend itself to such structural manipulations.

Assay

Development by the NHI scientists of a sensitive radioimmunoassay technique for determining small, physiological amounts of the hormone in blood, has opened the door to a conclusive evaluation of thyrocalcitonin's importance in normal bone and mineral metabolism of man, and a full appreciation of its role in various disease states characterized by excessive production or deficiency of the hormone.

According to this technique, partially purified pig thyrocalcitonin is injected into guinea pigs to stimulate the formation of antibodies. Guinea pig serum containing these antibodies is harvested. Pure thyrocalcitonin, labelled with a radioactive compound, is combined with these antibodies and becomes bound to them. To a measured amount of this combination, the scientists add the blood sample for assay. The thyrocalcitonin in the blood sample displaces or frees some of the radioactive hormone. The resulting ratio of radioactive bound to free hormone is an accurate index of how much thyrocalcitonin is contained in the blood sample.

The "Now" Hormone

With this technique, which has 1,000 times the sensitivity of bioassay methods, the NHI scientists were able to detect, for the first time in any normal animal, the minute quantities of thyrocalcitonin (less than one ten-millionth of an ounce per pint of blood) continuously secreted into the blood of intact rabbits, and to measure the rapidly increasing amounts of hormone released in response to transfusions of a calcium solution. No hormone was detected in animals subjected to surgical removal of their thyroid glands, but was found in extracts of the glands. Thus the studies confirm the thyroid origin of thyrocalcitonin in the rabbit, and show that its production is triggered by increased blood-calcium levels. Tests with the assay in man have shown that a certain form of thyroid cancer produces excessive quantities of thyrocalcitonin, a finding that may explain many of the symptoms of this disorder.

Clinical Studies

These studies have strengthened the probability, currently under study by a number of clinics, that thyrocalcitonin has value in treating patients suffering from certain diseases characterized by softening and weakening of the bones, as well as in combatting high blood calcium levels. The blood assay should prove useful in monitoring blood levels of the hormone during such therapeutic use.

In one NHI patient, afflicted with widespread cancer of the parathyroid glands and extensive destruction of bone (uncontrollable by conventional therapy), blood calcium has been maintained at normal levels for a period of 5 months, and bone lesions healed, by only intermittent treatment with small amounts of the highly purified hormone preparation supplied by Armour Pharmaceutical Company. This and other clinical studies were performed by the NHI Laboratory of Clinical Endocrinology, headed by Dr. Frederic C. Bartter.

Thus, the importance of thyrocalcitonin in the normal mineral metabolism of man and its role in various disease states as well as its therapeutic value should be more fully appreciated in coming months through the continuation of these extensive, worldwide research efforts on this hormone, whose existence was unknown only a few short years ago.—NHI, Bethesda, Md.

IMMUNIZATIONS

During the past several months the Bureau of Medicine and Surgery has received numerous reports that personnel being processed at West Coast POE's are delinquent in their immunizations. The vast

majority of these delinquencies appear to involve smallpox vaccination.

Your attention is invited to the recent *tri-service* directive on immunization requirements, designated in the Navy as BUMED Instruction 6230.1E. This Instruction requires that all personnel departing the United States have a smallpox vaccination within one year of their departure. Furthermore, smallpox vaccination is required annually while outside the United States.

All activities should check an individual's health record and his International Certificates of Vaccination (PHS Form 731, Rev 9-66) to insure that all necessary immunizations are completed, *and properly recorded*, prior to detachment from the parent station.

Regarding the recording of immunizations on PHS Form 731, the actual signature of the medical officer is required for smallpox, yellow fever and cholera vaccines. The Department of Defense immunization stamp must also be affixed. In addition, entries for yellow fever must specify the origin and batch number of vaccine. Additional information required for smallpox verification includes: (1) date must be expressed as day, month and year; for example, 5 May 1968; (2) results of primary vaccination; (3) type of vaccine use: freeze-dried or frozen; and, (4) origin and batch number of vaccine.

In Southeast Asia, the other immunizations which may be required include: typhoid, tetanus-diphtheria, influenza, cholera, plague, and gamma globulin. Requirement for this last-named agent may be found in BUMED Instruction 6230.13B.—PrevMedDiv, BuMed.

BUMED FILM RELEASES

The following new films can be found in Naval Hospital Film Libraries:

MN-10488—*The Surgical Team in Amphibious Support*—16mm motion picture—color, sound, 21 minutes—1967. Depicts composition and movement of surgical team supply block, organization of the team, and activities aboard, including preparation of an operating room and the receiving of casualties, both simulated and real, during a Marine landing.

MN-10394—*Infectious Hepatitis: Unwanted Souvenir*—16mm motion picture—color, sound, 19 minutes—1968. Film is aimed at Navy personnel and dependents living overseas, and on liberty overseas. Explains how infectious hepatitis affects its victims and how it is spread. Gives guides for eating in public restaurants and for preparing food at home and aboard ship.

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